IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Confirmation No. 2325
YOSHITAKE et al.	Atty. Ref.: 1050-4
Serial No. 10/594,436	T.C. / Art Unit: 1611
Filed: September 26, 2006	Examiner: K.S. Orwig

FOR: CONTROLLED-RELEASE PHARMACEUTICAL COMPOSITION AND METHOD FOR PRODUCING THE SAME

DECLARATION OF DR. SHIGERU AOKI

I, Shigeru Aoki of Kawashimamidori-machi, Kakamigahara City, Gifu, Japan 501-6195, declare the following:

1. In 1981, I earned a Bachelor's degree from Gifu Pharmaceutical University.

2. In 1981, I enrolled in graduate school at Gifu Pharmaceutical University, and earned Master's degree in 1983. Master's thesis is entitled *Preparation of Spherically Agglomerated Crystals of Aminophylline by Spherical Crystallization Technique.*

3. From 1983 to the present, I was employed by Eisai Co., Ltd., the assignee of this patent application, where I have been studying the formulation of solid dosage forms in Eisai's Formulation Research Laboratories.

4. In 1995, I was awarded a Ph.D. degree by Gifu Pharmaceutical University. My thesis is entitled *Development of Sustained Release Matrix Tablet Used Novel Mixture of Polymers and Paddle Beads Dissolution Method.*

5. On information and belief, I understand that the claims of this patent application are directed to a controlled-release pharmaceutical composition comprising (i) a core containing an acid-unstable physiologically active substance, a disintegrant, and an alkaline additive and (ii) a release-controlling coating that covers the core. The coating contains a water-insoluble polymer, an enteric polymer, and a hydrophobic wax. In the coating, the amount of hydrophobic wax is 20 to 35 wt% based on the coating's weight.

6. On information and belief, I understand that the Examiner has not allowed the claims because he alleges they would have been obvious, but he invited the submission of evidence to prove criticality of the amount of hydrophobic wax in the claimed range.

7. I have reviewed the references cited by the Examiner in the Office Action. None of them teach or suggest that the amount of hydrophobic wax in the release-controlling

coating is critical for a pharmaceutical composition's release characteristics. Thus, controlling the pharmaceutical composition's release characteristics by limiting the amount of hydrophobic wax in the release-controlling coating would not have been predicted from the evidence provided by the Examiner.

8. I conclude that the claimed range of hydrophobic wax from 20 wt% to 35 wt% is critical for the composition's release characteristics. Facts supporting my opinion are set forth below.

9. Since the results discussed below (e.g., release characteristics) would not have been predicted from the evidence provided by the Examiner, I conclude that they are unexpected and therefore the claims of this patent application would not have been obvious. The analysis supporting my opinion is explained below.

10. Here, the relationship between the amount of hydrophobic wax (e.g., magnesium stearate) in a release-controlling coating and the dissolution properties of a composition was studied. It was confirmed that magnesium stearate from 20 wt% to 35% (based on the weight of the release-controlling coating) is critical for the composition's properties. When the amount of magnesium stearate was lower than this range, the dispersed components aggregate in the coating suspension and thereby variation in dissolution lag time is undesirably increased. On the other hand, when the amount of magnesium stearate was higher than this range, the release-controlling coating is weakened, the acid resistance of the physiologically active substance is not ensured, and a suitable dissolution lag time is not obtained. The following experiments were performed.

11. Production of Core Tablets

Formulation and charge amount of core tablets produced for the study are listed in Table 1. Granulation was carried out using a 100 L supermixer (SM-100) at a blade rotation speed of 490 rpm for 5 min. Moisture in granules was removed using a shelf-type drier at 50°C for 23.5 hr. Loss on drying (LOD) was 0.75%. After drying, the dried granules were sized at 2000 rpm by a power mill using a 1.5 mmϕ screen size. Sized granules and raw materials for an external additive were blended at 20 rpm for 50 min using a 50 L tumbler mixer. Blended granules were finished using a rotary tabletting machine (AP-15) under a pressure of 500 kgf and rotation speed of 45 rpm to give a core tablet of 5 mmϕ (lot W011200).

Table 1: Formulation and charge amount of granulation step

Name of Raw Material	Formulation (mg/tablet)	Charge Amount (kg)
(Granulation portion)		
Rabeprazole sodium	5.0	1.1
D-Mannitol	33.6	7.392
Crospovidone (XL)	12	2.64
Sodium hydroxide	0.5	0.11
Hydroxypropylcellulose (HPC-L)	2.5	0.55
Ethanol anhydrous	q.s.	4.4
(External additive portion)		
Crospovidone (XL)	1.5	0.33
Magnesium stearate	0.9	0.198
Total solid content	56.0	12.32

12. Production of Undercoated Tablets

The above-described core tablets were divided into two portions. Two batches of undercoating were carried out (lots W011200-1 and W011200-2). Formulation and charge amount of the undercoating suspension are listed in Table 2. Covering the core tablets was carried out using Type 48 Aquacoater (AQC-48T). Undercoating conditions are listed in Table 3.

Table 2: Formulation and charge amount of undercoating liquid

Name of Raw Material	Formulation (mg/tablet)	Charge Amount (kg)
Ethylcellulose (EC10)	1.06	0.318
Hydroxypropylcellulose (HPC-L)	1.8	0.540
Magnesium stearate	0.84	0.252
Ethanol anhydrous	q.s.	16.000
Total solid content	3.7	1.110

Table 3: Undercoating conditions

Parameter	Production Condition
Dissolution	Polytron 7000 rpm for 10 min
Dispersion	Polytron 7000 rpm for 10 min
Charge amount of core tablet	Approximately 5 kg
Inlet air volume	4.0 m^3/min
Inlet air temperature	60°C
Spray gun	AT type, One piece
Spray Rate	25 mL/min (Initial 10 min) → 30 mL/min
Spray air	Air pressure: 0 3 MPa
	Atomize air volume: 150 NL/min Pattern air volume: 30 NL/min
Pan rotation	17 rpm
Spray gun distance	10 cm

13. Production of Release-Controlling Coating Tablets

Charge amount and composition ratio of the coating suspension are listed in Table 4. Coating was carried out using AQC-48T. Coating conditions are listed in Table 5. When the composition ratio of a hydrophobic wax such as magnesium stearate was 10% based on the weight of the release-controlling coating (W011200-A), the dispersed components in the coating suspension aggregated within minutes after its preparation. Thus, coating could not be accomplished. But such aggregation could be suppressed by cooling the coating suspension during its preparation and the release-controlling coating process. On the other hand, when the composition ratio of magnesium stearate was 50% based on the weight of the release-controlling coating (W011200-D), many of the tablets produced had cracks on the surface of the release-controlling coating film.

Table 4: Formulation and composition ratio of pulsatile coating suspension

Lot	W011200-A		W011200-B		W011200-E		W011200-D	
	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
Methacrylic acid-methyl methacrylate copolymer (Eudragit L100)	340	34.3	340	30.4	340	24.8	340	19.0
Ethylcellulose (EC10)	340	34.3	340	30.4	340	24.8	340	19.0
Talc	100	10.1	100	8.9	100	7.3	100	5.6
Titanium dioxide	60	6.1	60	5.4	60	4.4	60	3.4
Cetyl alcohol	50	5.1	50	4.5	50	3.6	50	2.8
Magnesium stearate	100	10.1	230	20.5	480	35.0	900	50.3
Ethanol anhydrous	11385	-	12880	-	15755	-	20585	-

Table 5: Release-controlling coating conditions

Parameter	Production Condition
Dissolution	Polytron 7000 rpm for 10 min
Dispersion	Polytron 7000 rpm for 10 min
Charge amount of undercoat tablet	Approximately 2.5 kg
Inlet air volume	4.0 m^3/min
Inlet air temperature	65°C
Spray gun	AT type, One piece
Spray rate	25 mL/min (initial 10 min) → 50 mL/min
Spray air	Air pressure: 0.3 MPa Atomized air volume: 150 NL/min Pattern air volume: 30 NL/min
Pan rotation	17 rpm
Spray gun distance	10 cm

14. Dissolution Test at pH 6.8

One controlled-release formulation tablet having a coating amount of 14 mg was put into a 0.1 N hydrochloric acid solution (750 mL), and stirred for two hours using a paddle method (50 rpm). Thereafter, 250 mL of a 0.2 M sodium triphosphate solution was immediately added to adjust the pH of the solution to 6.8, and the dissolution test was continuously carried out. Sampling was carried out using a flow cell, absorbance was measured using an UV absorbance spectrometer (wavelength = 290 nm), and variation over time in the release percent of rabeprazole sodium was measured (n = 6). The lag time is represented by the time at which the drug initiates release in a test solution at pH 6.8.

15. Dissolution Test at pH 8.0

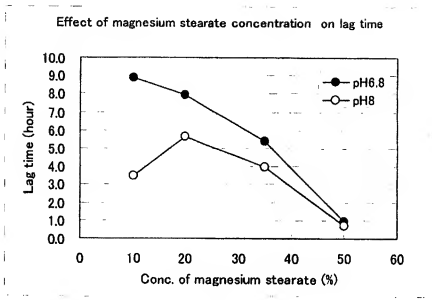
One controlled-release formulation tablet having a coating amount of 14 mg was put into a 0.1 N hydrochloric acid solution (700 mL), and stirred for two hours using a paddle method (50 rpm). Thereafter, 300 mL of a 0.57 mol/L solution of 2-amino-2-hydroxymethyl-1,3-propanediol solution was immediately added to adjust the pH of the solution to 8.0, and the dissolution test was continuously carried out. Sampling was carried out using a flow cell, absorbance was measured using an UV absorbance spectrometer (wavelength = 290 nm), and variation over time in the release percent of rabeprazole sodium was measured (n = 6). The lag time is represented by the time at which the drug initiates release in a test solution of pH 8.0.

16. The relationships between the composition ratio of magnesium stearate and the dissolution lag time in the buffers at pH 6.8 and pH 8.0 are shown in Table 6. It was confirmed that the difference in dissolution lag times between pH 6.8 and pH 8.0 tended to decrease according to the increase of the amount of magnesium stearate (Fig. 1B). The dissolution lag time gradually decreased after it is maximal at 20 wt% magnesium stearate. It was also shown at 50 wt% magnesium stearate that there is a lag time of only one hour and that acid resistance in enteric tablets for two hours could not be ensured. Since the hardness of the tablets decreases by incorporating magnesium stearate, it was presumed that excess magnesium stearate causes the decrease in film strength of the coating, which makes it difficult to ensure a sufficient lag time. Further, since many tablets were cracked during their coating, it is believed that damage to the release-controlling coating when the core is covered also contributed to this undesirable result. The

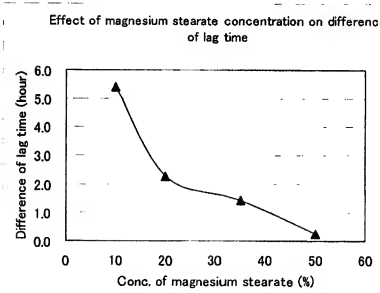
dissolution test was carried out by selecting tablets having no problem in appearance.

Table 6: Relationship between composition ratio of magnesium stearate (St-Mg) based on the weight of the release-controlling coating and dissolution lag time

St-Mg concentration	10%	20%	35%	50%
Coating amount	14 mg	14 mg	14 mg	14 mg
pH 6.8 Dissolution lag time (hr) (n=6)	9.17	8.00	5.33	0.83
	8.17	8.00	5.00	0.33
	9.67	8.17	5.50	0.83
	8.50	7.67	5.50	0.83
	9.33	7.67	5.17	1.00
	8.33	8.17	5.83	1.83
Mean	8.86	7.94	5.39	0.94
s.d.	0.61	0.23	0.29	0.49
pH 8 Dissolution lag time (hr) (n=6)	3.33	5.83	4.17	1.00
	3.50	5.17	4.00	0.33
	3.33	5.83	4.00	0.67
	3.67	5.67	3.83	0.67
	3.33	5.67	3.83	0.67
	3.50	5.83	3.83	0.83
Mean	3.44	5.67	3.94	0.69
s.d.	0.14	0.26	0.14	0.22
Difference in lag time between pHs (hr)	5.42	2.28	1.44	0.25



(A)



(B)

Figure 1: Relationship between composition ratio of magnesium stearate and dissolution lag time at each pH (A) and difference of lag time between pHs (B)

17. Variation of the dissolution lag time in accordance with variation of the composition ratio of magnesium stearate is shown in Fig. 2.

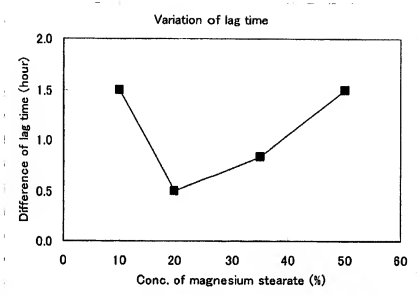


Figure 2: Relationship between composition ratio of hydrophobic wax such as magnesium stearate and variation of dissolution lag time

18. At 10% and 50%, the variation of the dissolution lag time at pH 6.8 was high. At 10%, solid contents tended to aggregate in the coating suspension, which is presumed to cause the variation in dissolution lag time. The cause of aggregation is considered to be formation of rod-shaped micelles by magnesium stearate, which is known to act as an ionic surfactant, and an ionic surfactant rapidly promotes formation of micelles at a certain temperature (Krafft point) or more to form rod-shaped micelles. Additionally, it is also known that liquid crystals such as those having hexagonal and laminar structures are formed when formation of micelles is further promoted. Because aggregation is suppressed by cooling of the coating suspension, it is believed that the Krafft point of magnesium stearate in ethanol exists at around room temperature. It is assumed that there is no aggregation when excess magnesium stearate (20 wt% or more) is present since magnesium stearate that is not involved in the formation of micelles acts as an inhibitor to inhibit formation of rod-shaped micelles. Meanwhile, when magnesium stearate is present at 50 wt%, lag time was within two hours and the required acid resistance of the physiologically active substance could not be ensured.

19. From the aforementioned results, I believe that it is critical to set the composition

ratio of hydrophobic wax in the range from 20 wt% to 35 wt% based on the weight of the release-controlling coating to reduce variation in dissolution lag time, to provide a lag time suitable for use of a physiologically active substance, and to achieve pulsatile controlled-release that is hardly affected by pH.

20. Therefore, based on the above facts and analysis, I conclude that requiring that the amount of hydrophobic wax in the coating is from 20 wt% to 35 wt% is sufficient to make the claims patentable over the references cited by the Examiner.

21. The undersigned declares that all statements made herein of my personal knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that any willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

Date: 27. May. 2010 Shigeru Aoki

Dr. Shigeru Aoki